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PrEP distribution in pharmacies: a systematic review

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Abstract

Introduction: Novel mechanisms of service delivery are needed to expand access to pre-exposure prophylaxis (PrEP) for HIV prevention to individuals at high risk. Providing PrEP directly through pharmacies could offer an additional option for reaching potential users with this safe and effective HIV prevention tool.

Methods: We conducted a systematic review of studies examining effectiveness, values and preferences of end users and providers, and cost of PrEP initiation and continuation through pharmacies (pharmacy access). Standardized methods were used to search, screen, and extract data from included studies.

Results: No articles met the inclusion criteria for the effectiveness review, for either PrEP initiation or continuation. However, seven "case studies" presenting non-comparative data from PrEP pharmacy programs demonstrated feasibility of this model in the United States. Eleven studies reported values and preferences of end users and providers. In the United States, Kenya, and South Africa, potential PrEP clients generally supported pharmacy access, though some preferred clinics. One study of actual PrEP pharmacy clients found all would "definitely recommend" the program. Six studies found pharmacists were generally supportive of offering PrEP; one study including doctors found more limited favor, while one study of diverse Kenyan stakeholders found broad support. Three studies reported cost data indicating client willingness to pay in the United States and Kenya and initial sustainability of a clinic financial model in the United States.

Conclusion: Provision of PrEP through pharmacies has been demonstrated to be feasible in the United States and acceptable to potential end users and stakeholders in multiple settings. Limited evidence on effectiveness and requirements for laboratory testing and assurance of high-quality services may limit enthusiasm for this approach. Further research is needed to determine if pharmacy access is a safe and effective way to help achieve global HIV prevention goals.

Keywords: PrEP, pharmacy, systematic review, values and preferences

Systematic review registration number: PROSPERO CRD42021231650

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Strengths and limitations of this study

- Novel service delivery mechanisms are needed to expand PrEP for HIV prevention to high-risk individuals, including providing PrEP through pharmacies.
- Seven case studies of PrEP pharmacy programs demonstrated feasibility in the US.
- In the US, Kenya, and South Africa, potential PrEP clients generally supported pharmacy access and actual PrEP pharmacy clients all would "definitely recommend" the program; pharmacists, doctors, and other stakeholders generally supported offering PrEP through pharmacies.
- Clients in the US and Kenya were willing to pay for PrEP through pharmacies, and initial sustainability of a clinic financial model for pharmacy access was demonstrated in the US.
- Pharmacy access to PrEP has been demonstrated to be feasible and acceptable, but further research is needed to assess the effectiveness of this service delivery approach and to assure high-quality services and pharmaceutical regulation to complement PrEP provision.

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Introduction

HIV pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs by HIV-uninfected individuals to prevent HIV infection. PrEP may either be taken orally in a daily pill (generally containing tenofovir plus emtricitabine), event-driven (at the time of sex), or in the form of a dapivirine vaginal ring; recent data suggest that long-acting injectable PrEP may soon be an additional option. The World Health Organization (WHO) recommends that people at substantial risk of HIV infection should be offered PrEP as an additional prevention choice as part of a combination prevention approach [1] which includes integration of sexual and reproductive health (SRH), HIV, and sexually transmitted infections (STI) services.[2]

Novel approaches to service delivery are being developed to expand PrEP access. Within clinical services, PrEP has been provided through community health clinics, sexually transmitted disease clinics, and primary care providers.[3] Community health workers have been trained to conduct PrEP outreach and provide referrals to PrEP prescription services.[4] There are also mobile applications that offer PrEP prescriptions from a qualified provider but without an in-person visit.[5] Making PrEP available outside of formal health facilities has the potential to reduce barriers to access, improve autonomy, and increase use and coverage of these effective HIV prevention options. It also may be a way to reach people who could benefit from PrEP but do not feel comfortable attending a clinic.

Pharmacies have been described as one area of untapped potential for PrEP delivery.[6-8] Pharmacies are often more accessible than health facilities, as they are usually conveniently located within communities, may have longer hours (including nights and weekends), and are available without an appointment. They also serve a wide range of health issues, so may reduce stigma associated with seeking HIV-related services. However, writing or filling PrEP prescriptions is not within pharmacists' scope of practice in many settings, so considering expansion of PrEP to pharmacies must be done with consideration of local regulatory guidelines.

This systematic review evaluates the evidence for distributing PrEP through pharmacies. We conducted this systematic review in the context of expanding the evidence base of WHO's normative guidance on self-care interventions.[9]. This guidance includes recommendations for over-the-counter pharmacy access to oral contraceptives as a means to expand access and coverage and is linked to WHO's competency-based training of pharmacists.[10] This review is also being conducted in response to the COVID-19 pandemic that has seen overstretched health systems and closures of medical facilities due to country-wide lockdowns globally [11] and where multi-month prescribing, including for clients initiating PrEP,[12] has been prioritized by WHO where appropriate.

Methods

This review addressed two related questions: whether PrEP *initiation* should happen in pharmacies, and whether PrEP *continuation* should happen in pharmacies. We reviewed the extant literature in three areas relevant to answering these questions: effectiveness of the intervention, values and preferences of end users and providers, and cost information. The review followed PRISMA guidelines [13] and the joint protocol for these questions was

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published on PROSPERO (CRD42021231650). Ethical approval was not required for this systematic review, since all data came from information freely available in the public domain (i.e. published articles or conference abstracts).

Effectiveness review

PICO question 1 - initiation

Should PrEP initiation be available following screening by a pharmacist, without a prescription?

Population: Individuals interested in PrEP
Intervention: PrEP access through a pharmacy without a prescription by a health care provider
Comparator: PrEP access by prescription from a health care provider
Outcomes:

(1) Uptake of PrEP (initial use)
(2) Continuation of PrEP (continued use or an intermittent pattern of use related to risk exposure)
(3) Correct use of PrEP (either daily or event-driven), including stopping and starting
(4) HIV acquisition/incidence
(5) Side effects, adverse events, and clinical harms (renal disease, sexually transmitted infection (STI) acquisition, STI treatment)
(6) Uptake of regular HIV testing (1 month after initiation and 3 monthly thereafter while taking PrEP – or if taking PrEP intermittently (seasons of risk) – prior to starting another period of PrEP)
(7) Self-efficacy, self-determination, autonomy, empowerment
(8) Social harms (e.g., coercion, violence (including intimate partner violence, violence from family members or community members, etc.), psychosocial harm, self-harm, etc.), and whether these harms were corrected/had redress available.

PICO question 2 - continuation

Should PrEP continuation be available from a pharmacist, without a prescription?

Population: Individuals taking PrEP
Intervention: PrEP access through a pharmacy without a prescription by a health care provider
Comparator: PrEP access by prescription from a health care provider
Outcomes:

(1) Use of PrEP (continued use or an intermittent pattern of use related to risk exposure)
(2) Correct use of PrEP (either daily or event-driven), including stopping and starting
(3) HIV acquisition/incidence
(4) Side effects, adverse events, and clinical harms (renal disease, STI acquisition, STI treatment)
(5) Uptake of regular HIV testing (1 month after initiation and 3 monthly thereafter while taking PrEP – or if taking PrEP intermittently (seasons of risk) – prior to starting another period of PrEP)
(6) Self-efficacy, self-determination, autonomy, empowerment

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(7) Social harms (e.g., coercion, violence (including intimate partner violence, violence from family members or community members, etc.), psychosocial harm, self-harm, etc.), and whether these harms were corrected/had redress available.

Inclusion criteria

To be included in the effectiveness review for either PICO question, an article had to meet the following criteria:

1) Study design that compared PrEP access through a pharmacy without a prescription by a health care provider to PrEP access by prescription from a health care provider. This included both randomized controlled trials, non-randomized controlled trials, and comparative observational studies (including prospective controlled cohort studies, cross-sectional studies, controlled before-after studies and interrupted time series) that compare individuals who received the intervention to those who did not.
2) Measured one or more of the outcomes listed above.
3) Published in a peer-reviewed journal or as a conference abstract.

If studies met all other criteria but did not present comparative data, we considered them "case studies". No restrictions were placed based on location of the intervention. No language restrictions were used on the search. Articles in English, French, Spanish, and Chinese were coded directly; articles in other languages were translated.

Search strategy

The following electronic databases were searched through the search date of November 30, 2020: PubMed, CINAHL, LILACS and EMBASE. We searched for ongoing RCTs through clinicaltrials.gov, the WHO International Clinical Trials Registry Platform, the Pan-African Clinical Trials Registry, and the Australian New Zealand Clinical Trials Registry. We searched abstracts from the following conferences: International AIDS Conference (AIDS), International AIDS Society Conference on HIV Science (IAS), International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention, HIV Research for Prevention, and Retroviruses and Opportunistic Infections (CROI), and HIV Research for Prevention (HIVR4P). Only abstracts available electronically were included. Secondary reference searching was conducted on all studies included in the review. Finally, selected experts in the field were contacted to identify additional articles not identified through other search methods.

Search terms

The following search strategy (PubMed) was adapted for entry into all computer databases. These search terms were used both for the main effectiveness systematic review (PICO questions) and for the values and preferences and cost reviews (described below).

("Pre-Exposure Prophylaxis" [Mesh] OR "pre-exposure prophylaxis" [tiab] OR "preexposure prophylaxis" [tiab] OR "antiretroviral prophylaxis" [tiab] OR "preexposure chemoprophylaxis" [tiab] OR PrEP [tiab])

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AND

("Nonprescription Drugs" [Mesh] OR nonprescription [tiab] OR "over the counter" [tiab] OR "over-the-counter" [tiab] OR "without a prescription" [tiab] OR "pharmacist-prescribed" [tiab] OR "pharmacy access" [tiab] OR "clinician-prescribed" [tiab] OR "physician-prescribed" [tiab] OR "GP-prescribed" [tiab] OR "general practitioner prescribed" [tiab] OR "without prescription" [tiab] OR "community pharmacy services" [Mesh] OR pharmacy [tiab] OR pharmacist [tiab])

AND

(HIV)

Screening abstracts

Titles, abstracts, citation information, and descriptor terms of citations identified through the search strategy were screened by a member of the senior study staff. Full-text articles were obtained of all selected abstracts and two independent reviewers assessed all full-text articles for eligibility to determine final study selection. Differences were resolved through consensus.

Data extraction and management

Data were extracted independently by two reviewers using standardized data extraction forms. Differences in data extraction were resolved through consensus and referral to a senior study team member from WHO when necessary.

The coding form collected the following information from each included study:

- Study identification: Author(s); type of citation; year of publication
- Study description: Study objectives; location; population characteristics; type of PrEP; PrEP initiation or continuation; study design; sample size; follow-up periods and loss to follow-up
- Outcomes: Analytic approach; outcome measures; comparison groups; effect sizes; confidence intervals; significance levels; conclusions; limitations

For randomized trials, risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias.[14] For non-randomized trials but comparative studies, study rigor was assessed using the Evidence Project 8-item checklist for intervention evaluations.[15]

Data analysis

Data were analyzed according to coding categories and outcomes. Where multiple studies reported the same comparative outcome, we planned to conduct meta-analysis using random-effects models to combine risk ratios with Comprehensive Meta-Analysis (CMA).

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We planned to stratify all PICO analyses by the following categories/subgroups (and intersections of these groups), where data were available:

- Type of PrEP (daily oral pill, event-driven, dapivirine vaginal ring, etc.)
- Populations (e.g. age, gender, race/ethnicity, key populations (men who have sex with men [MSM], sex workers, people who use drugs, transgender people, prisoners), etc.)
- Vulnerabilities (i.e. poverty, disability, literacy/educational level)
- High-income versus low or middle-income countries
- Condom use

We planned to summarize PICO findings in GRADE Evidence Profile tables using GRADEPro. Case studies were summarized descriptively according to coding categories and outcomes.

Values and preferences review

The same search terms were used to search and screen for studies on the values and preferences of end users and providers. Studies were included in this review if they presented primary data examining preferences of PrEP users, or individuals who might be or represent candidates for PrEP. We also included studies examining the values and preferences of healthcare providers, including pharmacists and community health workers. From these populations, we sought studies examining opinions, perspectives, values, and preferences related to PrEP access through pharmacies, or comparing PrEP access through pharmacies with other access points. We also considered issues related to age of availability, informed decision-making, coercion, seeking redress, and stigma and discrimination (anticipated and experienced) in accessing PrEP through pharmacies. These studies could be qualitative or quantitative in nature, but had to present primary data collection – think pieces and review articles were not included. Values and preferences literature were summarized qualitatively and were organized by study design and methodology, location, and population.

Cost review

The same search terms were used to search and screen for studies to be included in the cost review. Studies were included in this review if they presented primary data comparing costing, cost-effectiveness, cost-utility, or cost-benefit of PrEP initiation or continuation in pharmacies. Cost literature was summarized qualitatively. Cost literature was classified into four categories (health sector costs, other sector costs, patient/family costs, and productivity impacts) and within each category was organized by study design/methodology, location, and population.

Patient and public involvement

Feedback on the review protocol and analysis was received from the WHO patient safety working group. Patients were involved in a global survey of values and preferences conducted to inform the WHO guideline on self-care interventions; they thus play a significant role in the overall recommendation informed by this review.

Results

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Our search strategy yielded 253 unique records, of which 17 were ultimately included in the systematic review (Figure 1). Of these 17 studies, 0 were included in the effectiveness review but 7 were included as case studies, 11 were included in the values and preferences review, and 3 were included in the cost review.

Figure 1. PRISMA flow diagram showing disposition of citations through the search and screening process

Effectiveness review

No articles met the inclusion criteria for the primary PICO questions, either PrEP initiation or continuation.

However, we did identify seven "case studies" where PrEP was offered through pharmacies, but where there was no data comparing this to provision by prescription only. These were reported collectively in six articles and three abstracts.[16-24]

Table 1 presents descriptive information about the seven case studies. All seven case studies were conducted in urban areas in the United States of America (USA), although they came from diverse regions and served diverse populations. Most described operation through a collaborative practice agreement (CPA), where pharmacists operated under physician oversight to conduct activities that might otherwise be considered beyond their scope of practice. Most of the case studies described PrEP programs that provided client counseling and risk assessment, lab testing, and PrEP dispensing. In some cases, PrEP was initiated at the pharmacy and then patients had the option to continue elsewhere, while in other cases continuation occurred at the pharmacy.

Case studies provided descriptive data on the number of clients they served; some reported additional data on client demographics, test results, and PrEP continuation. Where distribution of clients by sex and sexual orientation was reported, programs said a majority of clients were male, and most were MSM. One study reported no differences in PrEP initiation or retention by client sex.[16] Client race varied substantially by setting, from 83.3% white [22] to 77% Black [16] to 47% Hispanic/Latino [17]. Insurance coverage varied, from 35% [16] to 80% [22] of PrEP clients.

One large case study from Seattle enrolled 695 clients on PrEP;[21] the remaining case studies reported smaller PrEP enrollments of between 50-200 clients. Across studies, among clients who were referred for PrEP or completed a PrEP screening visit, between 59% (n=56/95) [19] and 96% (n=51/53) [17] started PrEP or filled their prescription, often on the same day or within a week.

Follow-up rates varied. In one study, 43% (23/53) of clients who filled their prescription attended their initial clinical appointment within 6 weeks of obtaining PrEP [16]. Another study reported 81% (45/56) retention after 9 months.[19] The largest study reported a 25% drop-out rate and a mean duration of PrEP use of 302 days.[21]

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Three studies reported on HIV seroconversions among clients: two reported no seroconversions among PrEP clients,[19, 23, 24] and the third reported no seroconversions among active clients, but one seroconversion among a client who was lost to follow-up but then returned for PrEP and was diagnosed upon HIV testing at the return visit.[21] Two studies also reported HIV post-exposure prophylaxis (PEP): one reported started 2 of 56 patients on PEP prior to initiation of PrEP,[19] while another reported 6 clients receiving PEP.[17]

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Table 1. Description of articles included in the case study review

Study	Location	Description	Results
Ryan et al., 2018 [23, 24]	USA: Albuquerque, New Mexico	One of the first pharmacy-run HIV PrEP clinics in the USA was established in July 2015.	Over 200 patients have been seen at the PrEP clinic; the half-day weekly clinic generally sees 10-14 patients. There were no HIV seroconversions among those who started PrEP. Of the first 136 clients, 2 tested HIV-positive at baseline and 127 were started on PrEP (TDF/FDC). One discontinued due to side effects. No significant elevation in serum creatinine was noted over time. Adherence was average of <1 missed doses per month and a median compliance rate of 0.99.
Havens et al., 2019 [22]	USA: Omaha, Nebraska	Pharmacist-led PrEP (P-PrEP) allowed pharmacists to serve as PrEP providers through the utilization of a collaborative practice agreement (CPA). Pharmacists were provided additional education on HIV risk assessment, testing, risk reduction counseling, and administration of PrEP. Upon completion of training, P-PrEP pharmacists assumed responsibility for the PrEP care of individuals enrolled in P-PrEP through the CPA. Eligible P-PrEP participants were provided a 90-day F/TDF prescription. Participants had the option to continue PrEP care at the university-based HIV clinic or at 1 of 3 participating sites (community pharmacy, university-based primary care clinic, or community primary care clinic). Participants presented for follow-up visits every 3 months after PrEP initiation, and laboratory monitoring was performed. At all follow-up sites, a sample of whole blood by finger stick was collected for HIV screening and urine, rectal, and	60 participants enrolled in the P-PrEP program and started F/TDF. The majority, 91.7% (55/60), were men, 83.3% (50/60) were white, 80% (48/60) were commercially insured, and 89.8% (54/60) had completed some college or higher. The mean age of participants was 34 years (range, 20–61 years), and 88.3% (53/60) identified as MSM.

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		pharyngeal specimens were obtained for *Chlamydia trachomatis* and *Neisseria gonorrheae*.	
Khosropour et al., 2020 [16]	USA: Jackson, Mississippi	The pharmacist evaluated patients for medical contraindications to PrEP, but no baseline labs were obtained. The pharmacist provided a PrEP prescription and scheduled a clinical appointment for patients within 6 weeks, at which time they were evaluated by a clinician and completed baseline labs.	The pharmacist evaluated 69 patients for PrEP; 57% were MSM, 77% were black, and 65% were uninsured. All patients received a PrEP prescription; 83% received the prescription the same day and 97% received it within 5 days. Fifty-three (77%) of 69 clients filled the prescription; 87% of whom filled it within 1 week. Only 23 (43%) of 53 clients who filled their prescription attended their initial clinical appointment within 6 weeks of obtaining PrEP. There were no differences in PrEP initiation or retention by patient sex/gender.
Lopez et al., 2020 [17]	USA: San Francisco, California	A community pharmacy and the Department of Public Health (DPH) developed a CPA that allowed community pharmacists to initiate PrEP and PEP. Pharmacists were trained by DPH staff members on HIV testing and counseling and implementation of the PrEP protocol, including PEP initiation and STI testing. A DPH physician reviewed patients' charts regularly and communicated with PrEP pharmacists as needed.	In the first year, 6 patients received PEP and 53 patients completed a PrEP initiation visit, of whom 96% (n = 51) filled their prescription. Approximately 47% (n=24) of clients who started PrEP self-identified as Hispanic or Latino, 10% (n=5) were black or African American, and 82% (n=42) identified as MSM.
Sawkin & Shah, 2016 (abstract) [18]	USA: Kansas City, Missouri	Clinical pharmacists were trained and approved by the chief medical officer to provide HIV PrEP education and medication therapy management services outlined within a CPA. The protocol included details of screening patients and procedures for both baseline and follow-up visits for patients initiating PrEP therapy. Clinical protocol orders at the screening visit include rapid HIV testing, hepatitis C	In the first year, the PrEP clinic had more than 50 actively managed patients.

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		screening, urinalysis, pregnancy testing, complete blood count with differential, comprehensive metabolic profile, STI screening, and hepatitis B serology. Once deemed eligible for therapy after reviewing pertinent lab data, a pharmacist may prescribe TDF/FDC once daily for no more than 90 days to ensure medication safety and efficacy. Patients follow up every 3 months for routine labs including rapid HIV testing, a basic metabolic panel, and STD screening.	
Smith et al., 2019 (abstract) [19]	USA: Atlanta, Georgia	Pharmacy-based tele-PrEP program. PrEP services were provided directly to the community and through a consultative support program for all clinical sites within the hospital system. The key pilot interventions included developing a user-friendly electronic medical record-based PrEP order sets and brief provider education interventions in 6 primary care clinics.	Over 9 months, 95 referrals were received, 56 (59%) of whom started PrEP. Two patients were started on PEP prior to initiation of PrEP. Forty-five patients (81%) remained on PrEP. Six clients were diagnosed with 9 STIs on screening (4 syphilis, 2 gonorrhea, 2 chlamydia, 1 lymphogranuloma venereum). There were no HIV seroconversions in patients on PrEP.
Tung et al., 2017 (abstract) [20] and 2018 [21]	USA: Seattle, Washington state	The One-Step PrEP™ clinic, at a private pharmacy and under physician oversight (1 PGY1, 3 pharmacists, ancillary staff), provides PrEP with a single patient encounter. Pharmacists meet with patients individually, take a medical and sexual history, make a risk assessment, perform laboratory testing, provide patient education, and prescribe and dispense oral PrEP (TDF/FTC) when appropriate.	Of 714 patients evaluated, 695 (97.3%) initiated PrEP. Mean duration of PrEP use was 302 days. Same-day medication start: 513 (74%). Drop-out rate: 25%. STI diagnoses: 207 in 135 patients. HIV diagnoses: 2 at initial evaluation, 0 during active engagement, 1 after being LTFU.

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Values and Preferences Review

For the values and preferences review, 11 studies were identified, including one study that was also included in the case study review.[22, 25-30] The majority (n=8) were conducted in the USA, but two were conducted in Kenya, and one was conducted in South Africa. Seven used quantitative methods, generally cross-sectional surveys, while four used qualitative methods, generally in-depth interviews.

Table 2 presents descriptive data for the values and preferences studies, stratified by end users (including potential PrEP candidates, current PrEP users, or general populations), or pharmacists, healthcare providers and other professional stakeholders. Two studies included both potential end users and providers. Table 3 presents findings from the values and preferences studies. Six studies from the USA, Kenya, and South Africa found potential PrEP clients generally supported PrEP prescriptions in pharmacies, though some preferred clinics. For example, a discrete choice experiment focused on long-acting PrEP options among youth in South Africa noted that location of PrEP access was relatively less important than other attributes such as dosing frequency, pain, or insertion site, but that different populations expressed different location preferences: women preferred health clinic access, men who have sex with women only preferred community locations, and MSM preferred pharmacy or health clinics.[29] One study of current PrEP pharmacy users found all would "definitely recommend" the program.[22]. Six studies found pharmacists were generally supportive of offering PrEP;[22, 27, 31-34] one study including doctors found less support, and one study of diverse Kenyan stakeholders found broad support.[34] Benefits of pharmacy access included convenience, accessibility, and alignment with scope of work. Concerns included inadequate time, compensation for services, privacy, and training.

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Table 2. Descriptions of values and preferences studies

Study	Location	Population Description	Study design	Methods	Sample size (n)
End users					
Begnel et al., 2020 [25]	Kenya: Homa Bay, Kisii, Kisumu, Migori, Nyamira, and Siaya	Adults aged 18+	Quantitative	Cross-sectional SMS survey	2498
Crawford et al., 2020 [27]	USA: Atlanta area, Georgia	Adult MSM	Qualitative	Semi-structured in-depth interviews	8
Crawford et al., 2020 [26]	USA: Atlanta, Georgia	HIV- MSM not using PrEP	Quantitative	Cross-sectional survey	259
Havens et al., 2019 [22]	USA: Omaha, Nebraska	PrEP users	Quantitative	Cross-sectional survey in case study project	60
Lutz et al., 2020 [28]	USA: Arizona	HIV- PrEP clients and HIV+ ART clients	Quantitative	Cross-sectional survey	49
Minnis et al., 2020 [29]	South Africa: Nyanga and Masiphumelele, near Cape Town	PrEP-eligible youth aged 18-24	Quantitative	Discrete choice experiment	807
Zhu et al., 2020 [30]	USA: Washington, DC and Maryland	HIV- adults	Quantitative	Cross-sectional survey	117
Pharmacists and other professional stakeholders					

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Broekhuis et al., 2018 [31]	USA: Nebraska and Iowa	Pharmacists	Quantitative	Cross-sectional online survey	140
Crawford et al., 2020 [27]	USA: Atlanta area, Georgia	Pharmacists	Qualitative	Semi-structured in-depth interviews	6
Havens et al., 2019 [22]	USA: Omaha, Nebraska	Pharmacists	Quantitative	Cross-sectional survey in case study project	7
Hopkins et al., 2020 [32]	USA: Atlanta, Georgia	Pharmacists and pharmacy technicians	Qualitative	Semi-structured in-depth interviews	13
Koester et al., 2020 [33]	USA: California	Pharmacists, physicians, pharmacy representatives	Qualitative	Semi-structured phone interviews	11
Ortblad et al., 2020 [34]	Kenya: Nairobi	Stakeholders from PrEP regulatory, professional, healthcare service delivery, civil society, and research organizations	Qualitative	Focus groups	36

MSM: men who have sex with men; ART: antiretroviral therapy

Table 3. Key findings from values and preferences studies

Study	Location	Results
End users		

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Begnel et al., 2020 [25]	Kenya	When asked whether someone would be most likely to obtain PrEP at a clinic, pharmacy, kiosk, or other location, 44% chose clinics, 37% chose pharmacies, 17% chose kiosks, and 1% chose other.
Crawford et al., 2020 [26]	USA	Most participants (69%) were willing to discuss PrEP with pharmacy staff and 61.35% were willing to be screened for PrEP in pharmacy. There were no differences by race, after accounting for PrEP interest.
Crawford et al., 2020 [27]	USA	Most MSM supported in-pharmacy STI, HIV, and PrEP screenings and dissemination. Benefits included convenience and accessibility. Participants wanted to ensure privacy, confidentiality, and welcoming staff for MSM.
Havens et al., 2019 [22]	USA	At 6-month follow-up, all of the survey respondents stated they would definitely recommend the P-PrEP program.
Lutz et al., 2020 [28]	USA	93.9% were comfortable seeing a pharmacist to discuss PrEP, and 93.9% were comfortable having a pharmacist test for HIV before starting PrEP. 83.7% were comfortable having a pharmacist prescribe PrEP, although only 4 participants (8.2%) strongly agreed.
Minnis et al., 2020 [29]	South Africa	In this discrete choice experiment about hypothetical long-acting PrEP options, "where PrEP is available" was relatively less important than other attributes such as dosing frequency, pain, or injection site. Females preferred using a product that was offered at a health clinic over accessing it at a pharmacy ($p < 0.001$). Among males, men who have sex with women only had somewhat more preference for availability at a community location compared with a pharmacy and health clinic, whereas MSM held opposite views with pharmacy or health clinic preferred over a community location ($p = 0.01$).
Zhu et al., 2020 [30]	USA	Most participants supported pharmacists prescribing PrEP (Mean 4.0 (SD = 1.0), range 3.9 to 4.1 on a scale of 1-5 with 5 strongly agree). Most (58.1%) had no concerns; the most common concerns were “prefer to obtain a prescription from my doctor” (16.2%) and “privacy concerns” (15.4%). Participants were more likely to support pharmacy PrEP if they had previous interactions with pharmacists or if they had previously used PrEP (vs. non-users).
Pharmacists and other professional stakeholders		
Broekhuis et al., 2018 [31]	USA	Respondents were “moderately concerned” or “very concerned” about the following issues: time burden (61%), inadequate compensation for services (55%), outside skill set (39%), patient adherence to therapy (63%), loss to follow-up (56%), and promotion of antiretroviral drug resistance (51%).

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Crawford et al., 2020 [27]	USA	Although STI, HIV, and PrEP services were not currently available, all pharmacists expressed considerable support for providing these services within their pharmacies.
Havens et al., 2019 [22]	USA	The P-PrEP pharmacists felt comfortable performing point of care testing at all visits except on 1 occasion (0.7%, 1 of 139). 1 pharmacist at the community pharmacy site reported 3 occasions (2.2%) in which they felt uncomfortable conducting sexual histories during P-PrEP follow-up visits. Workflow disruption at the community pharmacy site was reported only once (0.7%) throughout the study.
Hopkins et al., 2020 [32]	USA	Pharmacists and pharmacy technicians expressed strong willingness and support for screening and dispensing PrEP in pharmacies. Both groups expressed concerns about the time and the resources needed to perform PrEP screening and dispensing. Technicians also reported concerns about privacy for patients as well as the need for community support and awareness of pharmacy-based PrEP screening, and they recommended scheduling of PrEP screening activities during a limited part of the day to facilitate screening. Pharmacists reported fewer barriers but a need for more training of pharmacy staff to assist with PrEP screening and dispensing implementation.
Koester et al., 2020 [33]	USA	Participants felt benefits included accessibility (longer pharmacy hours and accessible staff and locations), access to refill data to council on adherence, and alignment with other medications already given by pharmacists. Barriers included questions about who would cover costs and potential lack of privacy and training. Medical providers were not entirely supportive of expanding the pharmacists' scope of practice to include PrEP due to concerns about training to handle potential complications or other health issues that might present.
Ortblad et al., 2020 [34]	Kenya	Stakeholders were enthusiastic about a model for pharmacy-based PrEP delivery. Potential challenges identified included insufficient pharmacy provider knowledge and skills, regulatory hurdles to providing affordable HIV testing at pharmacies, and undefined pathways for PrEP procurement. Potential solutions included having pharmacy providers complete the Kenya Ministry of Health-approved PrEP training, use of a PrEP prescribing checklist with remote clinician oversight and provider-assisted HIV self-testing, and having the government provide PrEP and HIV self-testing kits to pharmacies during a pilot test.

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Cost review

Two of the case studies presented data about health sector costs and patient/family costs,[20-22] and one values and preferences article also examined willingness to pay for PrEP.[25] No studies looked at other sector costs or productivity impacts. Both case studies were conducted in the USA. For health sector costs, one clinic reported it recouped start-up costs in 9 months, and financial sustainability was dependent on the ability of pharmacists to bill insurance plans for their services.[20, 21] For patient/family costs, 98% of patients paid US$0 for their PrEP in one study, and in another, participants were split in willingness to pay US$20 or US$60 quarterly for PrEP visits.[20, 21] Finally, one article from Kenya found over half of participants were willing to pay for PrEP and 78% said the maximum they would pay for a month's supply was <US$5.[25]

Table 4. Description of articles included in the cost review

Study	Location	Results
Begnel et al., 2020 [25]	Kenya	Over half (61%) of participants were willing to pay for PrEP and 78% reported that the maximum amount they were willing to pay for a one-month supply was <$5.
Havens et al., 2019 [22]	USA: Omaha, Nebraska	Among participants who completed follow-up visits at the community pharmacy, half (6 of 12) stated they would be willing to pay at least $20 quarterly for continued PrEP visits and half (6 of 12) were willing to pay up to $60 quarterly.
Tung et al., 2017 (abstract) [20] and 2018 [21]	USA: Seattle, Washington state	In the 2017 abstract, 96% of patients (235/245) paid $0 for their PrEP. Initial startup costs were recouped after 9 months of operations. In the 2018 article, 98% of patients paid $0 for their PrEP (total n=695). Financial sustainability of the model was dependent on the ability of pharmacists to bill insurance plans for their services in accordance with local legislative changes requiring commercial insurances to recognize pharmacists as providers.

Discussion

This systematic review identified no studies for our primary PICO questions, indicating a paucity of evidence investigating the comparative effectiveness of pharmacy- versus provider-access to PrEP, for individuals initiating or continuing PrEP. However, we did identify seven non-comparative case studies which provide some limited evidence on the feasibility of pharmacy distribution of PrEP. Although all were from the USA, all found pharmacy-access PrEP to be a feasible service delivery model.

The evidence base identified in our review was largely focused on the USA, with just three values and preferences studies and one cost study from sub-Saharan African settings. This represents a critical gap in the literature given global differences in pharmacy regulation and capacity, particularly in many settings with high HIV prevalence. Pharmacies in the USA are subject to substantial regulations, and pharmacists generally receive high levels of training and

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oversight, which may enable provision of high-quality services for PrEP through pharmacies. In other settings, training and regulation may be more variable, making quality control more challenging. Notably, most of the case studies specifically described using CPAs which require physician oversight of pharmacist provision of PrEP. Most of the study pharmacies either had laboratory capacity or were well-connected with laboratories, providing an avenue for baseline tests and ongoing monitoring needed for PrEP. Where links with laboratories do not exist, it will be important to consider how they might be created to ensure appropriate support for PrEP initiation and continuation.[7] However, these models were found to be highly feasible with few adverse outcomes, warranting further research in a wider range of settings.

In terms of values and preferences, we found that actual or potential PrEP clients were generally supportive of pharmacy-access PrEP. Many included studies did not describe in-depth reasons for or against pharmacy PrEP. In the USA, MSM emphasized the importance of privacy, confidentiality, and having welcoming staff.[22, 27, 30] One study from South Africa highlighted the role of subgroup differences, finding that preferences for potential long-acting PrEP differed between women, MSM, and men who have sex with women.[29] These differences align with previous findings about user preferences for PrEP delivery more broadly.[35, 36] Further, even within subpopulations (e.g. women), heterogeneity is to be expected as user preferences may be shaped by geographic, economic, and sociocultural contexts.[37]

In particular, we found that pharmacy delivery of PrEP was highly accepted among marginalized groups, such as Black MSM in the south of the USA.[16, 26, 27] As these groups face critical barriers to accessing PrEP through more traditional modalities, pharmacy PrEP may be an important additional option for them.[38] Understanding the perspectives of other groups often excluded from research on PrEP users' values and preferences, such as transgender people, sex workers, or people who use drugs, is also critical.[35]

Evidence from providers indicated mixed support for pharmacy-access PrEP. Some had concerns about the added time associated with a new task, though one of our included case studies found that workflow disruption was minimal.[22] Concerns about insufficient training and skills to provide PrEP were common.[31-34] While guidelines and clinical requirements at PrEP visits vary across settings,[39] pharmacists require training and supervision to provide HIV and creatinine clearance testing at a minimum, along with pregnancy testing, STI screening, and other diagnostic tests depending on setting and population. Training may also be required regarding other aspects of integrated SRH, such as contraceptive provision or referral for people at risk of violence. For instance, lockdowns during the COVID-19 pandemic have limited access to health services, and task sharing to pharmacists can support a range of health interventions. The WHO Academy [10] module on counselling and prescribing of contraception in pharmacies has developed competency-based learning for pharmacists which could be further extended to other health areas, including provision of PrEP. Along with training and supervision, strategies to support laboratory access – whether on-site or elsewhere – will be key to offering PrEP through pharmacies. This might require changes to supply chain systems to ensure uninterrupted supply of PrEP medications for pharmacies, as well as changes to health management information systems to ensure that pharmacy-level activities can be captured. Furthermore, monitoring of

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pharmacy-access PrEP would have to become part of routine monitoring efforts in order to help ensure quality service provision.

Two of our included studies assessed client willingness to pay for pharmacy-access PrEP. Willingness to pay ranged from US$5 per month in Kenya [25] to as much as US$20 per month in the USA [22]. In terms of overall financial sustainability of the PrEP pharmacy model, in the USA, one study found this was achievable but entirely dependent on insurance billing. Since costs and willingness to pay will vary substantially by income, setting, and health system or insurance/reimbursement structure, further research in this area is needed. Additional evidence could elucidate cost differences in countries where national health insurance programs partner with pharmacies, compared to those where government services are generally provided for free or at low-cost. Broadly, given the high HIV burden and rapid scale-up of PrEP in sub-Saharan Africa,[40, 41] more costing data from this region is needed. For example, some African PrEP programs have adopted models wherein service delivery costs are shared across interventions through shared service platforms.[42-44] It may be that integrating PrEP into pharmacies offers similar opportunities for cost-sharing across programs and interventions;[45] this warrants further exploration.

While the studies included in our review all focused on daily oral PrEP except for one hypothetical values and preferences study on long-acting injectable PrEP, the monthly dapivirine vaginal ring is included in the WHO list of prequalified products and in recent WHO guidelines [46] as an additional prevention choice for women. Its high safety profile and low systemic absorption reduce requirements for laboratory monitoring may make pharmacy delivery and option for established women users. Long-acting injectable PrEP (cabotegravir), which is given by intramuscular injection every 8 weeks, is likely to gain regulatory approval and could potentially be considered in the future for pharmacy provision, if complexities with HIV testing and other implementation issues are resolved. Long-acting injectable PrEP formulations have been viewed favorably by potential end-users.[47] Future studies should consider not only the safety and effectiveness of delivering long-acting PrEP products such as the dapivirine vaginal ring and long-acting injectable PrEP at pharmacies, but also user and provider preferences around this delivery option. These interventions might also be considered as part of a broader package of SRH-related services that could be managed to the pharmacy-level, which might help maximize efficiencies and minimize stigma associated with standalone HIV interventions.

Our review had several strengths and limitations. We conducted a comprehensive search for articles not only on effectiveness, but also on values and preferences of end users and providers as well as cost data. However, our focus on peer-reviewed articles and conference abstracts may have missed some relevant information from program reports or other grey literature. Our conclusions are also limited because nearly all the evidence identified in our review came from the USA, except for a few studies from Kenya and South Africa. Future research should continue to examine the potential for pharmacy provision of PrEP in resource-limited settings.

Conclusions

Overall, we found that while pharmacy distribution of PrEP has been shown to be feasible in some studies in the USA and valued by end users in small studies, there is a lack of evidence

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around its effectiveness or its adaptability to low- and middle-income settings. As PrEP services continue to expand worldwide, additional research and programmatic efforts into pharmacy delivery are warranted. The services, staffing, infrastructure, and regulation of pharmacies varies considerably between and within countries; if PrEP products are to be delivered through these settings, minimum service requirements and staff training needs will need to be considered. With the increasing roll-out of PrEP across regions, more evidence from safety monitoring may reduce laboratory monitoring requirements, and the COVID-19 pandemic has led to adaptations to support continuation of PrEP delivery such as the use of HIV self-testing, virtual platforms, and telemedicine support. Future implementation research could explore how these could be incorporated into future PrEP pharmacy models. This evidence base should be informed by variation across contexts, screening and laboratory requirements, and values and preferences of affected populations and health workers. Privacy, confidentiality, and quality of services will be important to ensure for all clients. Overall, pharmacy access may be a promising strategy for expanding access to PrEP, improving equity, and helping to respect, protect and fulfil the right to health.

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Contributions: MN conceptualized the study, following discussion with RB. CK and PTY designed the protocol, with feedback from MN, RB, and LF. PTY ran the database search and oversaw the search, screening, full text review, and data extraction process. CK and KA drafted the manuscript. All authors reviewed the draft, provided critical review, and read and approved the final manuscript. The corresponding author, as guarantor, accepts full responsibility for the finished article has access to any data and controlled the decision to publish. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

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Data availability statement: Extracted data are available on request to the corresponding author.

Transparency declaration: The corresponding author, as guarantor, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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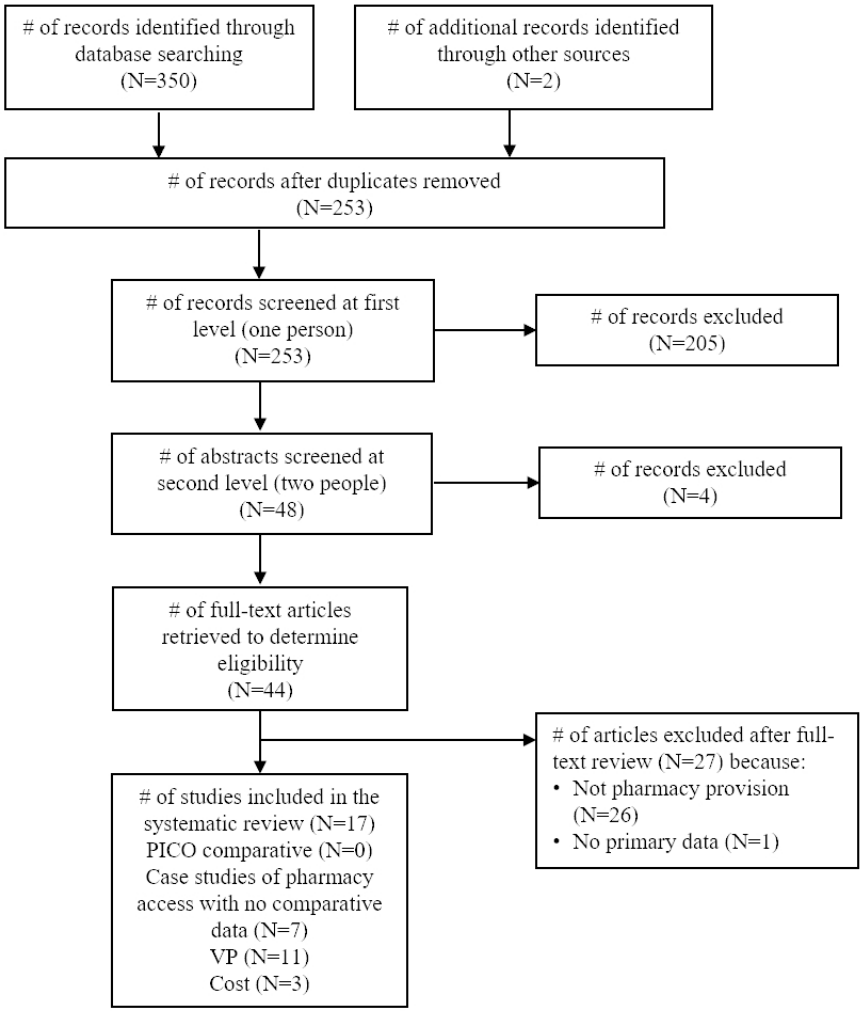

Figure 1. PRISMA flow diagram showing disposition of citations through the search and screening process

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6-7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

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PrEP distribution in pharmacies: a systematic review

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Abstract

Introduction: Novel mechanisms of service delivery are needed to expand access to pre-exposure prophylaxis (PrEP) for HIV prevention. Providing PrEP directly through pharmacies could offer an additional option for reaching potential users.

Methods: We conducted a systematic review of studies examining effectiveness, values and preferences of end users and health workers, and cost of PrEP initiation and continuation through pharmacies (pharmacy access). We searched PubMed, CINAHL, LILACS and EMBASE through December 2, 2020. We also searched clinical trial registries and recent HIV conference abstracts. Standardized methods were used to search, screen, and extract data from included studies.

Results: No studies met the inclusion criteria for the effectiveness review, for either PrEP initiation or continuation. However, six "case studies" presenting non-comparative data from PrEP pharmacy programs demonstrated feasibility of this model in the United States (US). Eleven studies reported values and preferences of end users and health workers. In the US, Kenya, and South Africa, potential PrEP clients generally supported pharmacy access, though some preferred clinics. One study of PrEP pharmacy clients found all would "definitely recommend" the program. Six studies found pharmacists were generally supportive of offering PrEP; one study including doctors found more limited favor, while one study of diverse Kenyan stakeholders found broad support. Three studies reported cost data indicating client willingness to pay in the US and Kenya and initial sustainability of a clinic financial model in the US.

Conclusion: Provision of PrEP through pharmacies has been demonstrated to be feasible in the US and acceptable to potential end users and stakeholders in multiple settings. Limited evidence on effectiveness and requirements for laboratory testing and assurance of high-quality services may limit enthusiasm for this approach. Further research is needed to determine if pharmacy access is a safe and effective way to help achieve global HIV prevention goals.

Keywords: PrEP, pharmacy, systematic review, values and preferences

Systematic review registration number: PROSPERO CRD42021231650

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Strengths and limitations of this study

- This systematic review used a comprehensive search for articles not only on the effectiveness of PrEP distribution through pharmacies, but also on costs of this model and values and preferences of end users and health workers.
- Because this is a rapidly growing field, we may have missed new publications or articles which used terms which were not in our search strategy.
- The generalizability of our findings globally may be limited, since nearly all evidence included in our review came from the USA besides a few studies from Kenya and South Africa.

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Introduction

HIV pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs by HIV-uninfected individuals to prevent HIV infection. PrEP may either be taken orally in a daily pill (generally containing tenofovir plus emtricitabine), event-driven (at the time of sex), or in the form of a dapivirine vaginal ring; recent data suggest that long-acting injectable PrEP may soon be an additional option. However, not all forms of PrEP are available in all settings globally; in most low-income countries, only daily oral PrEP is available. The World Health Organization (WHO) recommends that people at substantial risk of HIV infection should be offered PrEP as an additional prevention choice as part of a combination prevention approach [1] which includes integration of sexual and reproductive health (SRH), HIV, and sexually transmitted infections (STI) services.[2]

Novel approaches to service delivery are being developed to expand PrEP access. Within clinical services, PrEP has been provided through community health clinics, sexually transmitted disease clinics, and primary care providers.[3] Community health workers have been trained to conduct PrEP outreach and provide referrals to PrEP prescription services.[4] There are also mobile applications that offer PrEP prescriptions from a qualified health worker but without an in-person visit.[5] Making PrEP available outside of formal health facilities has the potential to reduce barriers to access, improve autonomy, and increase use and coverage of these effective HIV prevention options. It also may be a way to reach people who could benefit from PrEP but do not feel comfortable attending a clinic.

Pharmacies have been described as one area of untapped potential for PrEP delivery.[6-8] Pharmacies are often more accessible than health facilities, as they are usually conveniently located within communities, may have longer hours (including nights and weekends), and are available without an appointment. They also serve a wide range of health issues, so may reduce stigma associated with seeking HIV-related services. However, writing or filling PrEP prescriptions is not within pharmacists' scope of practice in many settings, so considering expansion of PrEP to pharmacies must be done with consideration of local regulatory guidelines.

This systematic review evaluates the evidence for distributing PrEP through pharmacies. We conducted this systematic review in the context of expanding the evidence base of WHO's normative guidance on self-care interventions.[9]. This guidance includes recommendations for over-the-counter pharmacy access to oral contraceptives as a means to expand access and coverage and is linked to WHO's competency-based training of pharmacists.[10] This review is also being conducted in response to the COVID-19 pandemic that has seen overstretched health systems and closures of medical facilities due to country-wide lockdowns globally [11] and where multi-month prescribing, including for clients initiating PrEP,[12] has been prioritized by WHO where appropriate.

Methods

This review addressed two related questions: whether PrEP *initiation* should happen in pharmacies, and whether PrEP *continuation* should happen in pharmacies. We focused on in-person pharmacy initation and continuation, and excluded telemedicine-based approaches. We

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reviewed the extant literature in three areas relevant to answering these questions: effectiveness of the intervention, values and preferences of end users and health workers, and cost information. The review followed PRISMA guidelines [13] and the joint protocol for these questions was published on PROSPERO (CRD42021231650). Ethical approval was not required for this systematic review, since all data came from information freely available in the public domain (i.e. published articles or conference abstracts).

Effectiveness review

PICO question 1 - initiation

Should PrEP initiation be available following screening by a pharmacist, without a prescription?

Population: Individuals interested in PrEP
Intervention: PrEP access through a pharmacy without a prescription by a health worker (defined as a non-pharmacist health worker)
Comparator: PrEP access by prescription from a health worker
Outcomes:

(1) Uptake of PrEP (initial use)
(2) Continuation of PrEP (continued use or an intermittent pattern of use related to risk exposure)
(3) Correct use of PrEP (either daily or event-driven), including stopping and starting
(4) HIV acquisition/incidence
(5) Side effects, adverse events, and clinical harms (renal disease, sexually transmitted infection (STI) acquisition, STI treatment)
(6) Uptake of regular HIV testing (1 month after initiation and 3 monthly thereafter while taking PrEP – or if taking PrEP intermittently (seasons of risk) – prior to starting another period of PrEP)
(7) Self-efficacy, self-determination, autonomy, empowerment
(8) Social harms (e.g., coercion, violence (including intimate partner violence, violence from family members or community members, etc.), psychosocial harm, self-harm, etc.), and whether these harms were corrected/had redress available.

PICO question 2 - continuation

Should PrEP continuation be available from a pharmacist, without a prescription?

Population: Individuals taking PrEP
Intervention: PrEP access through a pharmacy without a prescription by a health worker
Comparator: PrEP access by prescription from a health worker
Outcomes:

(1) Use of PrEP (continued use or an intermittent pattern of use related to risk exposure)
(2) Correct use of PrEP (either daily or event-driven), including stopping and starting
(3) HIV acquisition/incidence
(4) Side effects, adverse events, and clinical harms (renal disease, STI acquisition, STI treatment)

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(5) Uptake of regular HIV testing (1 month after initiation and 3 monthly thereafter while taking PrEP – or if taking PrEP intermittently (seasons of risk) – prior to starting another period of PrEP)
(6) Self-efficacy, self-determination, autonomy, empowerment
(7) Social harms (e.g., coercion, violence (including intimate partner violence, violence from family members or community members, etc.), psychosocial harm, self-harm, etc.), and whether these harms were corrected/had redress available.

Inclusion criteria

To be included in the effectiveness review for either PICO question, an article had to meet the following criteria:

1) Study design that compared PrEP access through a pharmacy without a prescription by a health worker to PrEP access by prescription from a health worker. This included both randomized controlled trials, non-randomized controlled trials, and comparative observational studies (including prospective controlled cohort studies, cross-sectional studies, controlled before-after studies and interrupted time series) that compare individuals who received the intervention to those who did not.
2) Measured one or more of the outcomes listed above.
3) Published in a peer-reviewed journal or as a conference abstract.

If studies met all other criteria but did not present comparative data, we considered them "case studies". No restrictions were placed based on location of the intervention. No language restrictions were used on the search. Articles in English, French, Spanish, and Chinese were coded directly; articles in other languages were translated.

Search strategy

The following electronic databases were searched through the search date of December 2, 2020: PubMed, CINAHL, LILACS and EMBASE. We searched for ongoing RCTs through clinicaltrials.gov, the WHO International Clinical Trials Registry Platform, the Pan-African Clinical Trials Registry, and the Australian New Zealand Clinical Trials Registry. We searched abstracts from the following conferences: International AIDS Conference (AIDS), International AIDS Society Conference on HIV Science (IAS), International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention, HIV Research for Prevention, and Retroviruses and Opportunistic Infections (CROI), and HIV Research for Prevention (HIVR4P). Only abstracts available electronically were included. Secondary reference searching was conducted on all studies included in the review. Finally, selected experts in the field were contacted to identify additional articles not identified through other search methods. The full search strategy for databases, registries, and conference websites can be found in Appendix A.

Screening abstracts

Titles, abstracts, citation information, and descriptor terms of citations identified through the search strategy were screened by a member of the senior study staff. Full-text articles were

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obtained of all selected abstracts and two independent reviewers assessed all full-text articles for eligibility to determine final study selection. Differences were resolved through consensus.

Data extraction and management

Data were extracted independently by two reviewers using standardized data extraction forms. Differences in data extraction were resolved through consensus and referral to a senior study team member from WHO when necessary.

The coding form collected the following information from each included study:

- Study identification: Author(s); type of citation; year of publication
- Study description: Study objectives; location; population characteristics; type of PrEP; PrEP initiation or continuation; study design; sample size; follow-up periods and loss to follow-up
- Outcomes: Analytic approach; outcome measures; comparison groups; effect sizes; confidence intervals; significance levels; conclusions; limitations

For randomized trials, risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias.[14] For non-randomized trials but comparative studies, study rigor was assessed using the Evidence Project 8-item checklist for intervention evaluations.[15]

Data analysis

Data were analyzed according to coding categories and outcomes. Where multiple studies reported the same comparative outcome, we planned to conduct meta-analysis using random-effects models to combine risk ratios with Comprehensive Meta-Analysis (CMA).

We planned to stratify all PICO analyses by the following categories/subgroups (and intersections of these groups), where data were available:

- Type of PrEP (daily oral pill, event-driven, dapivirine vaginal ring, etc.)
- Populations (e.g. age, gender, race/ethnicity, key populations (men who have sex with men [MSM], sex workers, people who use drugs, transgender people, prisoners), etc.)
- Vulnerabilities (i.e. poverty, disability, literacy/educational level)
- High-income versus low or middle-income countries
- Condom use

We planned to summarize PICO findings in GRADE Evidence Profile tables using GRADEPro. Case studies were summarized descriptively according to coding categories and outcomes.

Values and preferences review

The same search terms were used to search and screen for studies on the values and preferences of end users and health workers. Studies were included in this review if they presented primary data examining preferences of PrEP users, or individuals who might be or represent candidates

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for PrEP. We also included studies examining the values and preferences of health workers, including pharmacists and community health workers. From these populations, we sought studies examining opinions, perspectives, values, and preferences related to PrEP access through pharmacies, or comparing PrEP access through pharmacies with other access points. We also considered issues related to age of availability, informed decision-making, coercion, seeking redress, and stigma and discrimination (anticipated and experienced) in accessing PrEP through pharmacies. These studies could be qualitative or quantitative in nature, but had to present primary data collection – think pieces and review articles were not included. Values and preferences literature were summarized qualitatively and were organized by study design and methodology, location, and population.

Cost review

The same search terms were used to search and screen for studies to be included in the cost review. Studies were included in this review if they presented primary data comparing costing, cost-effectiveness, cost-utility, or cost-benefit of PrEP initiation or continuation in pharmacies. Cost literature was summarized qualitatively. Cost literature was classified into four categories (health sector costs, other sector costs, patient/family costs, and productivity impacts) and within each category was organized by study design/methodology, location, and population.

Patient and public involvement

Feedback on the review protocol and analysis was received from the WHO patient safety working group. Patients were involved in a global survey of values and preferences conducted to inform the WHO guideline on self-care interventions; they thus play a significant role in the overall recommendation informed by this review.

Results

Our search strategy yielded 253 unique records, of which 16 were ultimately included in the systematic review (Figure 1). Of these 17 studies, 0 were included in the effectiveness review but 6 were included as case studies, 11 were included in the values and preferences review, and 3 were included in the cost review.

Figure 1. PRISMA flow diagram showing disposition of citations through the search and screening process

Effectiveness review

No articles met the inclusion criteria for the primary PICO questions, either PrEP initiation or continuation.

However, we did identify six "case studies" where PrEP was offered through pharmacies, but where there was no data comparing this to provision by prescription only. These were reported collectively in six articles and two abstracts.[16-23]

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Table 1 presents descriptive information about the six case studies. All six case studies were conducted in urban areas in the United States of America (USA), although they came from diverse regions and served diverse populations. Most described operation through a collaborative practice agreement (CPA), where pharmacists operated under physician oversight. Most of the case studies described PrEP programs that provided client counseling and risk assessment, lab testing, and PrEP dispensing. In some cases, PrEP was initiated at the pharmacy and then patients had the option to continue elsewhere, while in other cases continuation occurred at the pharmacy.

Case studies provided descriptive data on the number of clients they served; some reported additional data on client demographics, test results, and PrEP continuation. Where distribution of clients by sex and sexual orientation was reported, programs said a majority of clients were male, and most were MSM. One study reported no differences in PrEP initiation or retention by client sex.[16] Client race varied substantially by setting, from 83.3% white [21] to 77% Black [16] to 47% Hispanic/Latino [17]. Insurance coverage varied, from 35% [16] to 80% [21] of PrEP clients.

One large case study from Seattle enrolled 695 clients on PrEP;[20] the remaining case studies reported smaller PrEP enrollments of between 50-200 clients. Across studies, among clients who were referred for PrEP or completed a PrEP screening visit, between 74% [19 20] and 96% [17] started PrEP or filled their prescription, often on the same day or within a week.

Follow-up rates varied. In one study, 43% (23/53) of clients who filled their prescription attended their initial clinical appointment within 6 weeks of obtaining PrEP [16]. The largest study reported a 25% drop-out rate and a mean duration of PrEP use of 302 days.[20]

Two studies reported on HIV seroconversions among clients: onereported no seroconversions among PrEP clients,[22 23] and the other reported no seroconversions among active clients but a seroconversion among a client who was lost to follow-up but then returned for PrEP and was diagnosed upon HIV testing at the return visit.[20] One study also reported HIV post-exposure prophylaxis (PEP), noting that six clients received PEP prior to initiation of PrEP.[17]

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Table 1. Description of articles included in the case study review

Study	Location	Description	Results
Ryan et al., 2018 [22 23]	USA: Albuquerque, New Mexico	One of the first pharmacy-run HIV PrEP clinics in the USA was established in July 2015. The half-day weekly clinic generally sees 10-14 patients per week. Over 200 patients have been seen overall.	There were no HIV seroconversions among those who started PrEP. Of the first 136 clients, 2 tested HIV-positive at baseline and 127 were started on PrEP (TDF/FDC). One discontinued due to side effects. No significant elevation in serum creatinine was noted over time. Average adherence was <1 missed doses per month and a median compliance rate of 0.99.
Havens et al., 2019 [21]	USA: Omaha, Nebraska	Pharmacist-led PrEP (P-PrEP) allowed pharmacists to serve as PrEP providers through a collaborative practice agreement (CPA). Pharmacists received education on HIV risk assessment, testing, risk reduction counseling, and administration of PrEP. Eligible participants received a 90-day F/TDF prescription and had the option to continue PrEP care at the university-based HIV clinic or at 1 of 3 participating sites (community pharmacy, university-based primary care clinic, or community primary care clinic). Follow-up visits were every 3 months after PrEP initiation, and laboratory monitoring was performed, including screening for HIV, chlamydia, and gonorrhea.	60 participants enrolled in the P-PrEP program and started F/TDF. The majority, 91.7% (55/60), were men, 83.3% (50/60) were white, 80% (48/60) were commercially insured, and 89.8% (54/60) had completed some college or higher. The mean age of participants was 34 years (range, 20–61 years), and 88.3% (53/60) identified as MSM.
Khosropour et al., 2020 [16]	USA: Jackson, Mississippi	The pharmacist evaluated patients for medical contraindications to PrEP, but no baseline labs were obtained. The pharmacist provided a PrEP prescription and scheduled a clinical appointment for patients within 6 weeks, at which time they were evaluated by a clinician and completed baseline labs.	The pharmacist evaluated 69 patients for PrEP; 57% were MSM, 77% were black, and 65% were uninsured. All patients received a PrEP prescription; 83% the same day and 97% within 5 days. 53 (77%) of 69 clients filled the prescription; 87% of whom filled it within 1 week. Only 23 (43%) of 53

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			clients who filled their prescription attended their initial clinical appointment within 6 weeks. There were no differences in PrEP initiation or retention by patient sex/gender.
Lopez et al., 2020 [17]	USA: San Francisco, California	A community pharmacy and the Department of Public Health (DPH) developed a CPA that allowed community pharmacists to initiate PrEP and PEP. Pharmacists were trained by DPH staff members on HIV testing and counseling and implementation of the PrEP protocol, including PEP initiation and STI testing. A DPH physician reviewed patients' charts regularly and communicated with PrEP pharmacists as needed.	In the first year, 6 patients received PEP and 53 completed a PrEP initiation visit, of whom 96% (n = 51) filled their prescription. 47% (n=24) of clients who started PrEP self-identified as Hispanic or Latino, 10% (n=5) were black or African American, and 82% (n=42) identified as MSM.
Sawkin & Shah, 2016 (abstract) [18]	USA: Kansas City, Missouri	Clinical pharmacists were trained to provide PrEP education and medication management outlined within a CPA. The screening visit includes rapid HIV testing, hepatitis C screening, urinalysis, pregnancy testing, complete blood count with differential, comprehensive metabolic profile, STI screening, and hepatitis B serology. Once deemed eligible, pharmacists prescribe TDF/FDC for up to 90 days to ensure medication safety and efficacy. Patients return every 3 months for labs including rapid HIV testing, a basic metabolic panel, and STD screening.	In the first year, the PrEP clinic had more than 50 actively managed patients.
Tung et al., 2017 (abstract) [19] and 2018 [20]	USA: Seattle, Washington state	The One-Step PrEP™ clinic, at a private pharmacy and under physician oversight (1 PGY1, 3 pharmacists, ancillary staff), provides PrEP with a single patient encounter. Pharmacists meet with patients individually, take a medical and sexual history, make a risk assessment, perform laboratory testing, provide patient education, and prescribe and dispense oral PrEP (TDF/FTC) when appropriate.	Of 714 patients evaluated, 695 (97.3%) initiated PrEP. Mean duration of PrEP use was 302 days. Same-day medication start: 513 (74%). Drop-out rate: 25%. STI diagnoses: 207 in 135 patients. HIV diagnoses: 2 at initial evaluation, 0 during active engagement, 1 after being LTFU.

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Values and Preferences Review

For the values and preferences review, 11 studies were identified, including one study that was also included in the case study review.[21 24-29] The majority (n=8) were conducted in the USA, but two were conducted in Kenya, and one was conducted in South Africa. Seven used quantitative methods, generally cross-sectional surveys, while four used qualitative methods, generally in-depth interviews.

Table 2 presents descriptive data for the values and preferences studies, stratified by end users (including potential PrEP candidates, current PrEP users, or general populations), or pharmacists, health workers and other professional stakeholders. Two studies included both potential end users and health workers. Table 3 presents findings from the values and preferences studies. Six studies from the USA, Kenya, and South Africa found potential PrEP clients generally supported PrEP prescriptions in pharmacies, though some preferred clinics. For example, a discrete choice experiment focused on long-acting PrEP options among youth in South Africa noted that location of PrEP access was relatively less important than other attributes such as dosing frequency, pain, or insertion site, but that different populations expressed different location preferences: women preferred health clinic access, men who have sex with women only preferred community locations, and MSM preferred pharmacy or health clinics.[28] One study of current PrEP pharmacy users found all would "definitely recommend" the program.[21]. Six studies found pharmacists were generally supportive of offering PrEP;[21 26 30-33] one study including doctors found less support, and one study of diverse Kenyan stakeholders found broad support.[33] Benefits of pharmacy access included convenience, accessibility, and alignment with scope of work. Concerns included inadequate time, compensation for services, privacy, and training.

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Table 2. Descriptions of values and preferences studies

Study	Location	Population Description	Study design	Methods	Sample size (n)
End users					
Begnel et al., 2020 [24]	Kenya: Homa Bay, Kisii, Kisumu, Migori, Nyamira, and Siaya	Adults aged 18+	Quantitative	Cross-sectional SMS survey	2498
Crawford et al., 2020 [26]	USA: Atlanta area, Georgia	Adult MSM	Qualitative	Semi-structured in-depth interviews	8
Crawford et al., 2020 [25]	USA: Atlanta, Georgia	HIV- MSM not using PrEP	Quantitative	Cross-sectional survey	259
Havens et al., 2019 [21]	USA: Omaha, Nebraska	PrEP users	Quantitative	Cross-sectional survey in case study project	60
Lutz et al., 2020 [27]	USA: Arizona	HIV- PrEP clients and HIV+ ART clients	Quantitative	Cross-sectional survey	49
Minnis et al., 2020 [28]	South Africa: Nyanga and Masiphumelele, near Cape Town	PrEP-eligible youth aged 18-24	Quantitative	Discrete choice experiment	807
Zhu et al., 2020 [29]	USA: Washington, DC and Maryland	HIV- adults	Quantitative	Cross-sectional survey	117
Pharmacists and other professional stakeholders					

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Broekhuis et al., 2018 [30]	USA: Nebraska and Iowa	Pharmacists	Quantitative	Cross-sectional online survey	140
Crawford et al., 2020 [26]	USA: Atlanta area, Georgia	Pharmacists	Qualitative	Semi-structured in-depth interviews	6
Havens et al., 2019 [21]	USA: Omaha, Nebraska	Pharmacists	Quantitative	Cross-sectional survey in case study project	7
Hopkins et al., 2020 [31]	USA: Atlanta, Georgia	Pharmacists and pharmacy technicians	Qualitative	Semi-structured in-depth interviews	13
Koester et al., 2020 [32]	USA: California	Pharmacists, physicians, pharmacy representatives	Qualitative	Semi-structured phone interviews	11
Ortblad et al., 2020 [33]	Kenya: Nairobi	Stakeholders from PrEP regulatory, professional, healthcare service delivery, civil society, and research organizations	Qualitative	Focus groups	36

MSM: men who have sex with men; ART: antiretroviral therapy

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Table 3. Key findings from values and preferences studies

Study	Location	Results
End users		
Begnel et al., 2020 [24]	Kenya	When asked whether someone would be most likely to obtain PrEP at a clinic, pharmacy, kiosk, or other location, 44% chose clinics, 37% chose pharmacies, 17% chose kiosks, and 1% chose other.
Crawford et al., 2020 [25]	USA	Most participants (69%) were willing to discuss PrEP with pharmacy staff and 61.35% were willing to be screened for PrEP in pharmacy. There were no differences by race, after accounting for PrEP interest.
Crawford et al., 2020 [26]	USA	Most MSM supported in-pharmacy STI, HIV, and PrEP screenings and dissemination. Benefits included convenience and accessibility. Participants wanted to ensure privacy, confidentiality, and welcoming staff for MSM.
Havens et al., 2019 [21]	USA	At 6-month follow-up, all of the survey respondents stated they would definitely recommend the P-PrEP program.
Lutz et al., 2020 [27]	USA	93.9% were comfortable seeing a pharmacist to discuss PrEP, and 93.9% were comfortable having a pharmacist test for HIV before starting PrEP. 83.7% were comfortable having a pharmacist prescribe PrEP, although only 4 participants (8.2%) strongly agreed.
Minnis et al., 2020 [28]	South Africa	In this discrete choice experiment about hypothetical long-acting PrEP options, "where PrEP is available" was relatively less important than other attributes such as dosing frequency, pain, or injection site. Females preferred using a product that was offered at a health clinic over accessing it at a pharmacy ($p < 0.001$). Among males, men who have sex with women only had somewhat more preference for availability at a community location compared with a pharmacy and health clinic, whereas MSM held opposite views with pharmacy or health clinic preferred over a community location ($p = 0.01$).
Zhu et al., 2020 [29]	USA	Most participants supported pharmacists prescribing PrEP (Mean 4.0 (SD = 1.0), range 3.9 to 4.1 on a scale of 1-5 with 5 strongly agree). Most (58.1%) had no concerns; the most common concerns were “prefer to obtain a prescription from my doctor” (16.2%) and “privacy concerns” (15.4%). Participants were more likely to support pharmacy PrEP if they had previous interactions with pharmacists or if they had previously used PrEP (vs. non-users).
Pharmacists and other professional stakeholders		
Broekhuis et al., 2018 [30]	USA	Respondents were “moderately concerned” or “very concerned” about the following issues: time burden (61%), inadequate compensation for services (55%), outside skill set (39%), patient adherence to therapy (63%), loss to follow-up (56%), and promotion of antiretroviral drug resistance (51%).

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Crawford et al., 2020 [26]	USA	Although STI, HIV, and PrEP services were not currently available, all pharmacists expressed considerable support for providing these services within their pharmacies.
Havens et al., 2019 [21]	USA	The P-PrEP pharmacists felt comfortable performing point of care testing at all visits except on 1 occasion (0.7%, 1 of 139). 1 pharmacist at the community pharmacy site reported 3 occasions (2.2%) in which they felt uncomfortable conducting sexual histories during P-PrEP follow-up visits. Workflow disruption at the community pharmacy site was reported only once (0.7%) throughout the study.
Hopkins et al., 2020 [31]	USA	Pharmacists and pharmacy technicians expressed strong willingness and support for screening and dispensing PrEP in pharmacies. Both groups expressed concerns about the time and the resources needed to perform PrEP screening and dispensing. Technicians also reported concerns about privacy for patients as well as the need for community support and awareness of pharmacy-based PrEP screening, and they recommended scheduling of PrEP screening activities during a limited part of the day to facilitate screening. Pharmacists reported fewer barriers but a need for more training of pharmacy staff to assist with PrEP screening and dispensing implementation.
Koester et al., 2020 [32]	USA	Participants felt benefits included accessibility (longer pharmacy hours and accessible staff and locations), access to refill data to council on adherence, and alignment with other medications already given by pharmacists. Barriers included questions about who would cover costs and potential lack of privacy and training. Medical providers were not entirely supportive of expanding the pharmacists' scope of practice to include PrEP due to concerns about training to handle potential complications or other health issues that might present.
Ortblad et al., 2020 [33]	Kenya	Stakeholders were enthusiastic about a model for pharmacy-based PrEP delivery. Potential challenges identified included insufficient pharmacy provider knowledge and skills, regulatory hurdles to providing affordable HIV testing at pharmacies, and undefined pathways for PrEP procurement. Potential solutions included having pharmacy providers complete the Kenya Ministry of Health-approved PrEP training, use of a PrEP prescribing checklist with remote clinician oversight and provider-assisted HIV self-testing, and having the government provide PrEP and HIV self-testing kits to pharmacies during a pilot test.

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Cost review

Two of the case studies presented data about health sector costs and patient/family costs,[19-21] and one values and preferences article also examined willingness to pay for PrEP.[24] No studies looked at other sector costs or productivity impacts. Table 4 summarizes the three studies included in the costs review. Both case studies which presented cost data were conducted in the USA. For health sector costs, one clinic reported it recouped start-up costs in 9 months, and financial sustainability was dependent on the ability of pharmacists to bill insurance plans for their services.[19 20] For patient/family costs, 98% of patients paid US$0 for their PrEP in one study, and in another, participants were split in willingness to pay US$20 or US$60 quarterly for PrEP visits.[19 20] Finally, one article from Kenya found over half of participants were willing to pay for PrEP and 78% said the maximum they would pay for a month's supply was <US$5.[24]

Table 4. Description of articles included in the cost review

Study	Location	Results
Begnel et al., 2020 [24]	Kenya	Over half (61%) of participants were willing to pay for PrEP and 78% reported that the maximum amount they were willing to pay for a one-month supply was <$5.
Havens et al., 2019 [21]	USA: Omaha, Nebraska	Among participants who completed follow-up visits at the community pharmacy, half (6 of 12) stated they would be willing to pay at least $20 quarterly for continued PrEP visits and half (6 of 12) were willing to pay up to $60 quarterly.
Tung et al., 2017 (abstract) [19] and 2018 [20]	USA: Seattle, Washington state	In the 2017 abstract, 96% of patients (235/245) paid $0 for their PrEP. Initial startup costs were recouped after 9 months of operations. In the 2018 article, 98% of patients paid $0 for their PrEP (total n=695). Financial sustainability of the model was dependent on the ability of pharmacists to bill insurance plans for their services in accordance with local legislative changes requiring commercial insurances to recognize pharmacists as providers.

Discussion

This systematic review identified no studies for our primary PICO questions, indicating a paucity of evidence investigating the comparative effectiveness of pharmacy- versus provider-access to PrEP, for individuals initiating or continuing PrEP. However, we did identify six non-comparative case studies which provide some limited evidence on the feasibility of pharmacy distribution of PrEP. Although all were from the USA, all found pharmacy-access PrEP to be a feasible service delivery model.

The evidence base identified in our review was largely focused on the USA, with just three values and preferences studies and one cost study from sub-Saharan African settings. This represents a critical gap in the literature given global differences in pharmacy regulation and capacity, particularly in many settings with high HIV prevalence. Pharmacies in the USA are subject to substantial regulations, and pharmacists generally receive high levels of training and

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oversight, which may enable provision of high-quality services for PrEP through pharmacies. In other settings, training and regulation may be more variable, making quality control more challenging. Notably, most of the case studies specifically described using CPAs which require physician oversight of pharmacist provision of PrEP. Training may also vary significantly by type of health worker, as pharmacists (compared with nurses or physicians) typically receive more robust training in pharmacotherapy as well as monitoring for efficacy, toxicity and safety; the team-based approach to pharmacy distribution of PrEP may synergize the strengths of each type of health worker. Most of the study pharmacies either had laboratory capacity or were well-connected with laboratories, providing an avenue for baseline tests and ongoing monitoring needed for PrEP. Where links with laboratories do not exist, it will be important to consider how they might be created to ensure appropriate support for PrEP initiation and continuation.[7] In some settings, health systems have developed simplified laboratory testing for PrEP delivery, for example by waiving creatinine testing, or have allowed HIV self-testing for PrEP continuation. However, these models were found to be highly feasible with few adverse outcomes, warranting further research in a wider range of settings.

In terms of values and preferences, we found that actual or potential PrEP clients were generally supportive of pharmacy-access PrEP. Many included studies did not describe in-depth reasons for or against pharmacy PrEP. In the USA, MSM emphasized the importance of privacy, confidentiality, and having welcoming staff.[21 26 29] One study from South Africa highlighted the role of subgroup differences, finding that preferences for potential long-acting PrEP differed between women, MSM, and men who have sex with women.[28] These differences align with previous findings about user preferences for PrEP delivery more broadly.[34 35] Further, even within subpopulations (e.g. women), heterogeneity is to be expected as user preferences may be shaped by geographic, economic, and sociocultural contexts.[36]

In particular, we found that pharmacy delivery of PrEP was highly accepted among marginalized groups, such as Black MSM in the south of the USA.[16 25 26] As these groups face critical barriers to accessing PrEP through more traditional modalities, pharmacy PrEP may be an important additional option for them.[37] Understanding the perspectives of other groups often excluded from research on PrEP users' values and preferences, such as transgender people, sex workers, or people who use drugs, is also critical.[34]

Evidence from health workers indicated mixed support for pharmacy-access PrEP. Some had concerns about the added time associated with a new task, though one of our included case studies found that workflow disruption was minimal.[21] Concerns about insufficient training and skills to provide PrEP were common.[30-33] While guidelines and clinical requirements at PrEP visits vary across settings,[38] pharmacists require training and supervision to provide HIV and creatinine clearance testing at a minimum, along with pregnancy testing, STI screening, and other diagnostic tests depending on setting and population. Training may also be required regarding other aspects of integrated SRH, such as contraceptive provision or referral for people at risk of violence. For instance, lockdowns during the COVID-19 pandemic have limited access to health services, and task sharing to pharmacists can support a range of health interventions. The WHO Academy [10] module on counselling and prescribing of contraception in pharmacies has developed competency-based learning for pharmacists which could be further extended to other health areas, including provision of PrEP. Along with training and supervision, strategies to

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support laboratory access – whether on-site or elsewhere – will be key to offering PrEP through pharmacies. This might require changes to supply chain systems to ensure uninterrupted supply of PrEP medications for pharmacies, as well as changes to health management information systems to ensure that pharmacy-level activities can be captured. Furthermore, monitoring of pharmacy-access PrEP would have to become part of routine monitoring efforts in order to help ensure quality service provision.

Two of our included studies assessed client willingness to pay for pharmacy-access PrEP. Willingness to pay ranged from US$5 per month in Kenya [24] to as much as US$20 per month in the USA [21]. In terms of overall financial sustainability of the PrEP pharmacy model, in the USA, one study found this was achievable but entirely dependent on insurance billing. Since costs and willingness to pay will vary substantially by income, setting, and health system or insurance/reimbursement structure, further research in this area is needed. Additional evidence could elucidate cost differences in countries where national health insurance programs partner with pharmacies, compared to those where government services are generally provided for free or at low-cost. Broadly, given the high HIV burden and rapid scale-up of PrEP in sub-Saharan Africa,[39 40] more costing data from this region is needed. For example, some African PrEP programs have adopted models wherein service delivery costs are shared across interventions through shared service platforms.[41-43] It may be that integrating PrEP into pharmacies offers similar opportunities for cost-sharing across programs and interventions;[44] this warrants further exploration.

While the studies included in our review all focused on daily oral PrEP except for one hypothetical values and preferences study on long-acting injectable PrEP, the monthly dapivirine vaginal ring is included in the WHO list of prequalified products and in recent WHO guidelines [45] as an additional prevention choice for women. Its high safety profile and low systemic absorption reduce requirements for laboratory monitoring may make pharmacy delivery and option for established women users. Long-acting injectable PrEP (cabotegravir), which is given by intramuscular injection every 8 weeks, is likely to gain regulatory approval and could potentially be considered in the future for pharmacy provision, if complexities with HIV testing and other implementation issues are resolved. Long-acting injectable PrEP formulations have been viewed favorably by potential end-users.[46] Future studies should consider not only the safety and effectiveness of delivering long-acting PrEP products such as the dapivirine vaginal ring and long-acting injectable PrEP at pharmacies, but also end user and health worker preferences around this delivery option. These interventions might also be considered as part of a broader package of SRH-related services that could be managed to the pharmacy-level, which might help maximize efficiencies and minimize stigma associated with standalone HIV interventions.

Our review had several strengths and limitations. We conducted a comprehensive search for articles not only on effectiveness, but also on values and preferences of end users and health workers, as well as cost data. However, our focus on peer-reviewed articles and conference abstracts may have missed some relevant information from program reports or other grey literature. We missed the words "initiation", "initiate", and "initiated" in our search terms, but believe that most articles describing pharmacist initiation of PrEP would have used either "pharmacy" or "pharmacist" so would have been captured by our search. We also acknowledge

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that this is a new and rapidly growing field; we may have excluded articles which would have met our inclusion criteria but were published after our search date, including at least one acceptability and feasibility study conducted among clients and health workers in Kenya which reinforced our findings of support for expanding PrEP to retail pharmacies, though participants wanted to ensure that such services would be "private, respectful, safe, and affordable".[47] Our conclusions are also limited because nearly all the evidence identified in our review came from the USA, except for a few studies from Kenya and South Africa. Future research should continue to examine the potential for pharmacy provision of PrEP in resource-limited settings.

Conclusions

Overall, we found that while pharmacy distribution of PrEP has been shown to be feasible in some studies in the USA and valued by end users in small studies, there is a lack of evidence around its effectiveness or its adaptability to low- and middle-income settings. As PrEP services continue to expand worldwide, additional research and programmatic efforts into pharmacy delivery are warranted. The services, staffing, infrastructure, and regulation of pharmacies varies considerably between and within countries; if PrEP products are to be delivered through these settings, minimum service requirements and staff training needs will need to be considered. With the increasing roll-out of PrEP across regions, more evidence from safety monitoring may reduce laboratory monitoring requirements, and the COVID-19 pandemic has led to adaptations to support continuation of PrEP delivery such as the use of HIV self-testing, virtual platforms, and telemedicine support. Future implementation research could explore how these could be incorporated into future PrEP pharmacy models. This evidence base should be informed by variation across contexts, screening and laboratory requirements, and values and preferences of affected populations and health workers. Privacy, confidentiality, and quality of services will be important to ensure for all clients. Overall, pharmacy access may be a promising strategy for expanding access to PrEP, improving equity, and helping to respect, protect and fulfil the right to health.

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Data availability statement: Extracted data are available on request to the corresponding author.

Transparency declaration: The corresponding author, as guarantor, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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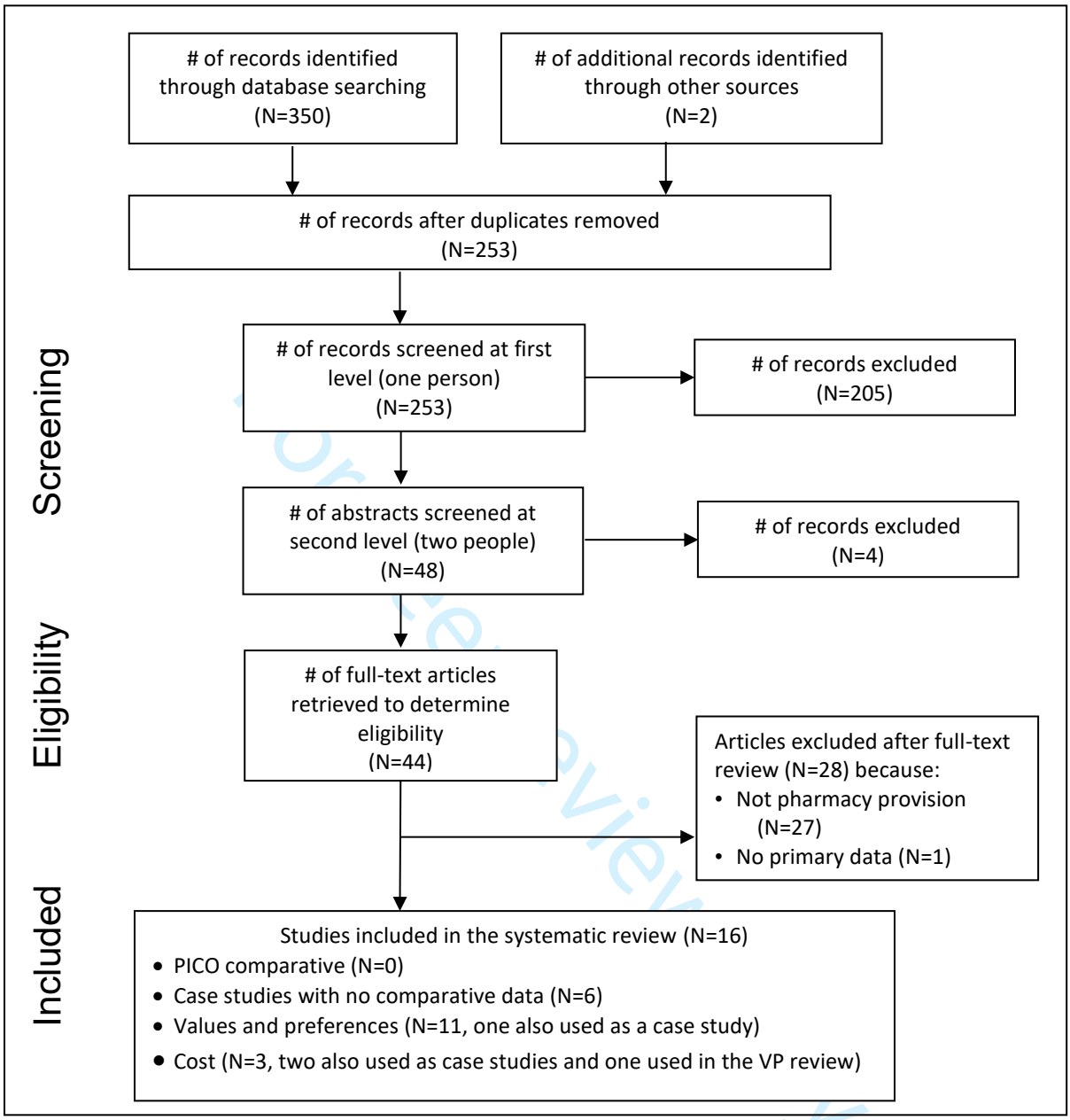
# of records identified through database searching (N=350)
# of additional records identified through other sources (N=2)
# of records after duplicates removed (N=253)
Screening
# of records screened at first level (one person) (N=253)
# of records excluded (N=205)
# of abstracts screened at second level (two people) (N=48)
# of records excluded (N=4)
Eligibility
# of full-text articles retrieved to determine eligibility (N=44)
Articles excluded after full-text review (N=28) because:
• Not pharmacy provision (N=27)
• No primary data (N=1)
Included
Studies included in the systematic review (N=16)
• PICO comparative (N=0)
• Case studies with no comparative data (N=6)
• Values and preferences (N=11, one also used as a case study)
• Cost (N=3, two also used as case studies and one used in the VP review)

PrEP distribution in pharmacies: a systematic review
Appendix A. Search strategy

Pubmed
("Pre-Exposure Prophylaxis" [Mesh] OR "pre-exposure prophylaxis" [tiab] OR "preexposure prophylaxis" [tiab] OR "antiretroviral prophylaxis" [tiab] OR "preexposure chemoprophylaxis" [tiab] OR PrEP [tiab]) AND ("Nonprescription Drugs" [Mesh] OR nonprescription [tiab] OR "over the counter" [tiab] OR "over-the-counter" [tiab] OR "without a prescription" [tiab] OR "pharmacist-prescribed" [tiab] OR "pharmacy access" [tiab] OR "clinician-prescribed" [tiab] OR "physician-prescribed" [tiab] OR "GP-prescribed" [tiab] OR "general practitioner prescribed" [tiab] OR "without prescription" [tiab] OR "community pharmacy services" [Mesh] OR pharmacy [tiab] OR pharmacist [tiab]) AND (HIV)

CINAHL
AB ("Pre-Exposure Prophylaxis" OR "preexposure prophylaxis" OR "antiretroviral prophylaxis" OR "preexposure chemoprophylaxis" OR PrEP) AND AB ("Nonprescription Drugs" OR nonprescription OR "over the counter" OR "over-the-counter" OR "without a prescription" OR "pharmacist-prescribed" OR "pharmacy access" OR "GP-prescribed" OR "general practitioner prescribed" OR "without prescription" OR "community pharmacy services" OR "pharmacy" OR "pharmacist") AND AB (HIV)

LILACS
Title/abstract/subject: ("Pre-Exposure Prophylaxis" OR "preexposure prophylaxis" OR "antiretroviral prophylaxis" OR "preexposure chemoprophylaxis" OR PrEP)

EMBASE
AB,TI,KW ('Pre-Exposure Prophylaxis' OR 'preexposure prophylaxis' OR 'antiretroviral prophylaxis' OR 'preexposure chemoprophylaxis' OR PrEP) AND AB,TI,KW ('Nonprescription Drugs' OR nonprescription OR 'over the counter' OR 'over-the-counter' OR 'without a prescription' OR 'pharmacist-prescribed' OR 'pharmacy access' OR 'GP-prescribed' OR 'general practitioner prescribed' OR 'without prescription' OR 'community pharmacy services' OR 'pharmacy' OR 'pharmacist') AND AB,TI,KW (HIV)

Clinicaltrials
https://clinicaltrials.gov/
1/15/2021
"PrEP" AND "Pharmacy"
"PrEP" AND "over the counter"
"Pre-Exposure Prophylaxis" AND "over the counter"
"Pre-Exposure Prophylaxis" AND "pharmacy"

WHO ICTRP
https://apps.who.int/trialsearch/
1/15/2021
Pre exposure prophylaxis AND HIV

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PACTR
http://www.pactr.org/
1/15/2021
pre exposure prophylaxis
PrEP

ANZCTR
https://www.anzctr.org.au/
1/15/2021
pre exposure prophylaxis
PrEP

Cochrane Library
https://www.cochranelibrary.com/search
1/15/2021
Pre exposure prophylaxis AND HIV
PrEP
PrEP AND Over-the-counter
PrEP AND Pharmacy

AIDS, 2020
https://www.aids2020.org/wp-content/uploads/2020/09/AIDS2020_Abstracts.pdf
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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6-7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	22

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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